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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/256,156	02/24/1999	STEPHEN GILLIES	LEX-003	9492

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EXAMINER	
HUNNICUTT, RACHEL KAPUST	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/256,156	GILLIES ET AL.	
	Examiner	Art Unit	
	Rachel K. Hunnicutt	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-8,10,27,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4* is/are allowed.

6)☒ Claim(s) *1,3,6-8,10,27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

Applicant's amendment filed July 8, 2004 if acknowledged. Claims 3 and 4 are amended. Claims 1, 3, 4, 6-8, 10, 27, 29, and 30 are pending and under consideration. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

The rejection of claims 1, 3, 6-8, 10, 29, and 30 under 35 U.S.C. 101 as being directed to non-statutory subject matter is withdrawn in view of Applicant's arguments.

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in response to Applicant's amendment to claim 4.

The rejection of claims 1, 3, 6-8, 10, 27, 29, and 30 under 35 U.S.C. 103(a) as being unpatentable over Gray *et al.* in view of Harvill *et al.* is withdrawn in response to Applicant's argument that there was no motivation to combine Gray *et al.* with Harvill *et al.*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-8, 10, 27, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding fusion proteins having decreased Fc receptor binding wherein the CH2 domain of IgG1 was deleted or mutated at Leu_{234}, Leu_{235}, Gly_{236}, Gly_{237}, Asn_{297}, or Pro_{331}, the CH2 domain of IgG3 was deleted or mutated at Leu_{281}, Leu_{282}, Gly_{283}, Gly_{284}, Asn_{344}, or Pro_{378}, or the entire IgG4 CH2 domain was used in place of an IgG1 CH2 domain, does not reasonably provide enablement for nucleic acids

encoding fusion proteins having any mutation or deletion in the CH2 domain or any portion of an IgG4 CH2 domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims encompass a large number of genetic modifications in the CH2 domain of an immunoglobulin, and the only common functional characteristic required is that the encoded protein have decreased Fc receptor binding. Applicants teach that mutating or deleting Leu_{234}, Leu_{235}, Gly_{236}, Gly_{237}, Asn_{297}, or Pro_{331} of the IgG1 constant region or Leu_{281}, Leu_{282}, Gly_{283}, Gly_{284}, Asn_{344}, or Pro_{378} of the IgG3 constant region can decrease Fc receptor binding (p. 3). Applicants also teach that fusion proteins having an IgG4 constant region have a longer circulating half-life than fusion proteins with an IgG1 constant region (p. 9). However, the claims encompass any substitution or deletion of any amino acid in an IgG1 or an IgG3 CH2 domain or any portion of an IgG4 CH2 domain. This encompasses hundreds of different variations of the CH2 domain. Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine, without undue experimentation, the positions in the CH2 domain the can be deleted or substituted or which portions of the IgG4 domain can be used in order to decrease Fc receptor binding.

The problem of predicting polypeptide structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide is extremely complex. While it is known that many amino acid substitutions are generally possible in any given polypeptide, the positions within the polypeptide's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Moreover, certain positions in the sequence are critical to the polypeptide's structure/function relationship,

such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites.

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on polypeptide structure and function, and the breadth of the claims which fail to recite any effective functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 1, 6-8, 10, 27, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus, *i.e.* polynucleotides encoding fusion proteins comprising a heavy chain of an immunoglobulin that has decreased Fc receptor binding. The genus includes heavy chains having any genetic modification. Applicants have disclosed fusion proteins comprising the entire IgG4 CH2 domain and mutations or deletions at Leu_{234}, Leu_{235}, Gly_{236}, Gly_{237}, Asn_{297}, or Pro_{331} of the IgG1 constant region or Leu_{281}, Leu_{282}, Gly_{283}, Gly_{284}, Asn_{344}, or Pro_{378} of the IgG3, but have not disclosed sufficient species for the broad genus of any genetic modification that results in decreased Fc receptor binding.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses hundreds of different CH2 domains with varying structures and functions. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus

of polypeptides. Furthermore, the prior art does not provide compensatory structural or correlative teaching sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Only once the heavy chains have been genetically modified and the fusion proteins expressed and assayed can a person of skill in the art determine that the heavy chain has decreased Fc receptor binding. Thus, no identifying characteristics or properties of the instant proteins are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, one of skill in the art would doubt that Applicants had possession of the claimed species at the time the application was filed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Claim Rejections - 35 USC § 103

Claims 1, 3, 6-8, 10, 27, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies *et al.* (1993, *Bioconjugate Chem.* 4: 230-235) in view of Gray *et al.*

(U.S. Patent No. 6,444,792). Claims 1, 29, and 30 are drawn to an antibody-based fusion proteins comprising a portion of an IgG1 or IgG3 CH2 domain with a mutation resulting in reduced binding affinity for an Fc receptor fused at its 3' end to a non-immunoglobulin protein. Claim 3 is drawn to an antibody-based fusion protein comprising a mutation at residue 234, 235, 236, 237 or 297 that results in decreased binding affinity for Fc receptors. Claim 6 is drawn to an antibody-based fusion protein comprising a mutation in a CH2 domain resulting in decreased binding affinity for FcγRI, FcγRII or FcγRIII. Claims 7-10 are drawn to an antibody-based fusion protein wherein the non-immunoglobulin protein is a cytokine such as the interleukin IL-2. Claim 27 is drawn to an antibody-based fusion protein comprising a portion of an IgG4 CH2 domain fused at its C-terminus to the N-terminus of a non-Ig protein.

Gillies *et al.* teach Ig-IL-2 fusion proteins wherein IL-2 is fused to the C-terminus of the immunoglobulin (p. 231, column 2). The purpose of the fusion protein was to obtain a molecule with a long circulating half-life that can target cytokines to tumors (p. 233, column 2). The immunoglobulin was being used for antigen recognition and for increasing the serum half-life of the cytokines. However, Gillies *et al.* teach that the Ig-IL2 fusion protein was cleared very quickly from circulation. Thus, while Gillies *et al.* teach an Ig-IL2 fusion protein, they do not teach one mutated so that it has an increased serum half-life.

Gray *et al.* teach antibody-based fusion proteins comprising a modified constant region and a second non-immunoglobulin protein (column 3). The immunoglobulin constant region may comprise a hinge region, a CH2 domain, and a CH3 domain from IgG1, IgG2, IgG3 or IgG4 (column 4, lines 15-17). Gray *et al.* teach the CH2 domain may be modified to reduce interactions with Fc receptors such as FcRI by modifying at least one residue at positions 234, 235, 236 or 237 by substitution, deletion or addition of amino acids (column 9, lines 60-64 and column 4, lines 24-33). Gray *et al.* teach that such modifications are useful for decreasing complement activation and phagocytosis of the fusion protein. It would have been obvious to one of ordinary skill in the art to combine the teachings of Gillies *et al.* and Gray *et al.* in order to generate antibody-based fusion proteins comprising IL-2 wherein the antibody-based fusion protein has reduced binding affinity for Fc receptors and an increased serum half-life. One of ordinary skill in the art would have been motivated to do so because Gillies *et al.* teach the utility of Ig-IL2 fusion proteins in targeting IL2 to tumors. Gillies *et al.* also teach that because the Ig-

IL2 fusion proteins are cleared so quickly from the bloodstream, constant infusion rather than bolus injection may be necessary in order to achieve clinical efficacy. The skilled artisan would have been motivated to combine the teachings of Gillies *et al.* and Gray *et al.* because Gray *et al.* teach that certain modifications within the CH2 domains can lead to increased serum half-life. One of ordinary skill in the art would have expected the modified fusion protein to be successful in targeting IL2 to tumors and to have a longer serum half-life than the fusion protein as taught by Gillies *et al.*

Claim 3 is further rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies *et al.* and Gray *et al.* in view of Winter *et al.* (U.S. Patent No. 5,624,821 cited in paper no. 26). Claim 3 is as stated above. The teachings of Gillies *et al.* and Gray *et al.* are as stated above. Gray *et al.* teach mutations at positions 234, 235, 236 and/or 237 may reduce interactions with Fc receptors, however Gray *et al.* do not teach any benefits of mutations at residue 297. Winter *et al.* teach that mutating residues 234, 235, 236 and/or 297 alters an effector function of an immunoglobulin as compared with an unmodified form (see column 5, lines 42-58; column 7, lines 21-28, and claim 1). It would have been obvious to a person of ordinary skill in the art to make an antibody-based fusion protein wherein the CH2 domain has a mutation occurring at residue 297 that results in reduced binding affinity for an Fc receptor. One of ordinary skill in the art would have been motivated to do so because Gray *et al.* teach the benefits of engineering antibody-based fusion proteins with reduced affinity for Fc receptors. Moreover, a person of ordinary skill in the art would have expected success in engineering the modified antibody-based fusion protein.

Conclusion

Claim 4 is allowed.

Claims 1, 3, 6-8, 10, 27, 29, and 30 are rejected.

The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

Kirkman *et al.* (1989), *Transplantation* 47(2): 327-330

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel K. Hunnicutt whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RKH
9/28/04

JANET ANDRES
PRIMARY EXAMINER